211 Fever, Chills, and Night Sweats

LAWRENCE DALL and JAMES F. STANFORD

Definition

In health, body temperature is regulated around a set point of 37 ± 1°C, and a circadian temperature rhythm exists in which the highest temperature of each day occurs around 6 P.M. The variance between the highest and lowest core temperature in a given day is usually no more than 1° to 1.5°C. This circadian rhythm may differ among individuals but should be consistent in each person. Relative to the core (blood) temperature, oral temperature tends to be about 0.4°C lower and axillary temperature up to 1°C lower, while rectal temperature, probably because of fecal bacterial metabolism, averages about 0.5°C higher.

Fever is a physiologic disorder in which the temperature is elevated above one's normal temperature. An elevated body temperature may accompany any condition in which exogenous or endogenous heat gain exceeds mechanisms of heat dissipation such as occurs with vigorous exercise, exposure to a warm ambient temperature, or the use of drugs that cause excess heat production or limit heat dissipation. In these situations the hypothalamic "thermostat" remains "set" in the normal range. In true fever, mechanisms to regulate the body temperature above the normal set point are actively operating.

In most patients with fever lasting 1 to 2 weeks, the etiology will be found or the fever will disappear. Occasionally, despite the history, physical examination, laboratory and radiologic procedures, fever (temperature above 38.3°C) will continue beyond 2 to 3 weeks without diagnosis. These patients are said to have *fever of undetermined origin* (FUO). Although the classic Petersdorf and Beeson definition still has utility, in this era of prospective payment medicine it can be modified to include careful outpatient documentation of fever and lack of diagnosis after careful outpatient evaluation. The critical aspects of any definition of FUO are documentation of fever (>38.3°C with a supervised electronic thermometer) and allowance of adequate time for the vast majority of self-limited viral illnesses to run their course.

Chills are the subjective reports of shivering or shaking associated with rapid changes in body temperature. They result from involuntary muscle contractions that occur in response to a sudden lowering of body temperature below the prevailing set point.

Night sweats are subjective reports of nocturnal sweating that results from an exaggeration of the normal circadian temperature rhythm.

Technique

A carefully obtained and detailed history is invaluable in the evaluation of febrile conditions. The etiology is often evident from the history and physical examination alone. While some patients will have taken their temperature with a thermometer, many will not have done so. Patients can usually relate the sensation of feeling warm and the frequent nonspecific accompanying symptoms of fatigue, myalgias, back pain, headache, and diaphoresis. Some patients, however, especially those with tuberculosis, occasional patients with drug fevers, and patients with other distracting unpleasant symptoms, may be unaware of temperatures as high as 39.4°C. A history of accompanying chills or night sweats should be sought. A sensation of chilliness is very common with fever from any cause and has little specificity, but an abrupt onset of fever with one or two hard chills (rigors) of teeth-chattering, bed-shaking intensity suggests an acute bacterial infection such as pneumococcal pneumonia.

The pattern of temperature elevation and the specific details of other associated symptoms should be obtained along with an accurate description of the initial onset of illness. Patients may begin their story with a recent dramatic change in their condition (e.g., high fever) when in actuality their illness began months earlier with, for example, weight loss, back pain, or other symptoms.

A careful travel history, exposure history (persons with fever, known infectious disease, animals, ticks, fresh or sea water, undercooked or unprocessed foods, toxins, etc.), sexual history, and family history may provide vital clues. Has the patient had any recent visits to the dentist or another doctor? Is the patient a health care professional, and what is their current state of mental health? Does the patient have any underlying conditions or take any medications that might interfere with thermoregulation? (Table 211.1).

When fevers persist and become fevers of undetermined origin, the careful and detailed history and physical examination are the clinician's most valuable tools. These must be performed repeatedly throughout the evaluation. Repeated questioning may reveal information that was not deemed pertinent by the patient on initial evaluation. Questioning of a relative, friend, or former physician can be quite enlightening. On physical examination particular attention should be given to skin lesions, funduscopic changes, organomegaly, nails, lymph nodes, heart auscultation, genitalia, and rectal examination. Physical findings may change dramatically during a hospitalization, and meticulous repetition may reveal the needed information.

In the patient with fever of undetermined origin, vague or trivial complaints and minor physical findings are often important. Avoid making the common mistake of overlooking, disregarding, or rejecting an obvious clue.

Basic Science

Fever has been recognized as one of the hallmarks of clinical disease since ancient times. Accurate recording of body temperature became possible in the eighteenth century when the Dutch inventor Farenheit introduced the thermometer.

Table 211.1
Drugs That Cause Fever

Most commonly
Amphotericin B
Antihistamines
Asparaginase
Barbiturates
Bleomycin sulfate
Methyldopa
Penicillin
Phenytoin sodium
Procainamide
Quinidine sulfate
Salicylates
Sulfonamides
Occasionally
Allopurinol
Azathioprine
Cephalosporins
Cimetidine
Cocaine derivatives
Hydralazine hydrochloride
Iodides
Isoniazid
Nitrofurantoin sodium
Para-aminosalicylic acid
Propylthiouracil
Rifampin
Streptokinase
Streptomycin sulfate
Vancomycin hydrochloride
Almost never
Digitalis
Chloramphenicol
Insulin
Tetracyclines

Source: Modified with permission of Lipsky BA, Hirshmann V. Drug fever. JAMA 1981;245:851–54.

In 1868, the German physician Wunderlich emphasized the clinical usefulness of recording body temperature based on his observations of 25,000 patients. Fever accompanies infectious as well as noninfectious diseases and holds a central role in the definition and pathogenesis of heat-related illnesses such as heat stroke. The pathogenesis, pathophysiology, and purpose of fever are becoming well delineated.

Most fevers are caused by infection, although many disease states can be responsible (e.g., central nervous system lesions, neoplasms, endocrine abnormalities, connective tissue diseases). Febrile states that are not secondary to disordered thermoregulation, like that seen in hypothalamic lesions, are due to the release of endogenous pyrogen.

Endogenous pyrogen (EP) acts on receptors in the thermoregulatory hypothalamus to cause fever. This fever production may be mediated by an increase in local prostaglandin (PGE_2) production, monoamines, cations such as sodium and calcium, or cyclic adenosine monophosphate. Exogenous stimuli of EP release from its source in monocytes, liver, spleen and lung macrophages, keratinocytes, polymorphonuclear cells, vascular endothelial, and smooth muscle cells, and kidney mesangial cells include: lipopolysaccharide (endotoxin) of gram-negative rods, viruses, other bacterial products, fungi, etiocholanolone, antigen–antibody complexes, polynucleotides, and other antigens. Viruses, tumors, and hypersensitivity reactions to drugs and other substances may stimulate EP release from monocytes indirectly via lymphokines secreted after interaction with sensitized lymphocytes.

Recently it has been discovered that there are actually three endogenous pyrogens that mediate fever—interleukin-1 (IL-1), tumor necrosis factor (TNF, cachetin), and interferon α. IL-1, which is identical to lymphocyte activating factor (LAF), in addition to inducing fever, modulates a large number of host defense responses including a mitogenic action on T lymphocytes, which results in increased generation of helper T cells, a reduction in plasma iron and zinc concentrations, neutrophilia, and increases in acute phase plasma proteins. Since many organisms require iron for growth, a fall in available plasma iron is to their detriment and has potentially great benefit to the host. TNF is similar to IL-1 in many of its properties but does not activate lymphocytes.

A number of factors (Table 211.2) may alter the normal thermoregulatory response. They may lead directly to hyperthermia (heat-related illness) or, in the case of EP-mediated fever, may be responsible for prolongation of fever and the development of extreme temperature elevations. Excess heat is dissipated by radiation, conduction, and convection via hypothalamic-mediated cutaneous vasodilation and increased cardiac output. Evaporation heat loss requires an intact sweating mechanism as well as hypothalamic input. When ambient air temperature becomes 35°C or higher, neither conduction nor radiation is effective. High humidity limits heat loss by vaporization.

Clinical Significance

Although the cause of fever is often evident from the history, physical examination, and initial laboratory and radiologic studies, sorting through the myriad causes in an organized approach is a formidable task for the clinician. The approach should be directed and well thought out.

The clinical usefulness of fever patterns is dubious, although there are some notable exceptions. There are five patterns: intermittent, remittent, continuous or sustained, hectic, and relapsing. With intermittent fever, the temperature is elevated but falls to normal (37.2°C or below) each day, while in a remittent fever the temperature falls each day but not to normal. In these two patterns the amplitude of temperature change is more than 0.3°C and less than 1.4°C. Either of the two patterns can be called hectic when the difference between peak and trough temperature is great (1.4°C or more). Sustained fever is a pattern in which there is little change (0.3°C or less) in the elevated temperature during a 24-hour period. In relapsing fever, a variant of the intermittent pattern, fever spikes are separated by days or weeks of intervening normal temperature.

Although not diagnostic, at times fever curves can be suggestive. Hectic fevers, because of wide swings in temperature, are often associated with chills and sweats. This pattern is thought to be very suggestive of an abscess or pyogenic infection such as pyelonephritis and ascending cholangitis, but may also be seen with tuberculosis, hypernephromas, lymphomas, and drug reactions.

Continuous or sustained fever is usually not associated with true chills or rigors. It is characteristic of typhoid fever or typhus, although commonly seen in bacterial endocarditis, tuberculosis, fungal disease, and bacterial pneumonia. Noninfectious etiologies include neoplasms, connective tissue disease, and drug fever.

Relapsing fevers may be seen in rat-bite fever, malaria,

Table 211.2
Thermoregulatory Factors Associated with Fever and Heat-related Illness

Exogenous heat gain
High ambient temperature
Extremes of age
Debilitating illnesses
Alcohol (peripheral vasodilation)
Increased heat production
Exercise and exertion
Improper training techniques
Fever and acute infection
Agitated and tremulous states
Parkinson's disease
Acute psychosis/mania
Drug withdrawal: alcohol, barbiturates, meprobamate
Drug overdose
Amphetamines
Hallucinogens (LSD)
Phencyclidine (PCP)
Severe salicylate overdose
Hyperthyroidism and thyroid medication
Impaired heat dissipation
Lack of acclimatization
Salt and water depletion
High ambient temperature
High humidity
Moderate to severe obesity
Heavy clothing
Cardiovascular disease
Neurologic disease (autonomic dysfunction, dementia, stroke, parkinsonism)
Drugs
Diuretics
Anticholinergics
Neuroleptics (phenothiazines, butyrophenones)
Antidepressants
Antihistamines
Antiparkinsonian agents
Beta blockers, alpha-methyldopa
Monoamine oxidase inhibitors
Sweat gland dysfunction
Cystic fibrosis
Scleroderma
Ectodermal dysplasia
Extensive post-burn scarring
Miliaria
Sweat gland necrosis secondary to barbiturate overdose or previous heat stroke
Potassium depletion
Miscellaneous
Diabetes mellitus
Malnutrition

Source: Modified with permission of Stine RJ. Heat illness. JACEP 1979;8:154–60.

cholangitis, infections with *Borrelia recurrentis*, Hodgkin's disease (Pel-Ebstein fever), and other neoplasms.

Historically, some diseases are described as having characteristic fever patterns. The double quotidian fever of gonococcal endocarditis has two spikes in a 24-hour period. Fever at 48-hour intervals suggests *Plasmodium vivax* or *P. ovale;* 72-hour intervals suggest *P. malariae,* while *P. falciparum* often has an unsynchronized intermittent fever.

Most fevers follow the usual diurnal pattern. Disseminated tuberculosis, typhoid fever, and polyarteritis nodosa are important exceptions in which reversal of the usual diurnal pattern ("typhus inversus" pattern) can be observed. A reversed pattern is also seen with old age and with salicylate ingestion.

Table 211.3
Causes of Relative Bradycardia

Factitious fever
Drug fever
Legionnaires' disease
Psittacosis
Typhoid fever
Mycoplasma pneumonia
Brucellosis
Dengue
Yellow fever
Tuberculous meningitis
Blackwater fever (Falciparum malaria with profound hemolysis)

Contrary to widely held beliefs, the height of temperature elevation has little diagnostic significance. Although thermoregulatory defects should certainly be thought of when temperatures exceed 40.5°C, infection, either alone (39%) or coexisting with a thermoregulatory defect (32%), has been found in 71% of patients with extreme (41.1°C or greater) pyrexia.

Drug fevers also may exceed 40.5°C and may simulate septicemia. Drugs causing fever (Table 211.1) may do so by administration-related mechanisms (e.g., amphotericin, phlebitis, fluid contamination), pharmacologic action of the drug (e.g., Jarish–Herxheimer reaction, tumor cell necrosis with chemotherapeutic agents), alteration of thermoregulation (see Table 211.2), idiosyncratic susceptibility (e.g., malignant hyperthermia), or drug-specific hypersensitivity (e.g., penicillin, methyldopa, quinidine). Patients with drug fever may appear well or quite ill and may or may not have a relative bradycardia. Rapid resolution of fever is seen with discontinuation of the medication in the vast majority of cases.

As a rule, the pulse rate rises about 15 beats/min for each degree centigrade of fever. When this expected rise is not seen, a relative bradycardia exists and, in the absence of beta-adrenergic blockers, suggests one of the diseases listed in Table 211.3.

Fever of undetermined origin is most often caused by an unusual manifestation of a common disease rather than a more exotic condition. Although the causes of fever of undetermined origin broadly span the categories of infectious and noninfectious disease listed in Table 211.4, two-thirds are caused by infectious and neoplastic diseases (30 to 40% and 30% respectively), while another 15% are hy-

Table 211.4
Causes of Fever of Unknown Origin

Bacterial infections
Spirochetal infections
Rickettsial infections
Chlamydial infections
Viruses
Fungi
Parasites
Neoplasms
Hypersensitivity and autoimmune diseases
Granulomatous diseases
Inherited diseases
Central nervous system causes
Drugs
Factitious fever

persensitivity related, autoimmune, or granulomatous, 10% miscellaneous, and 10 to 15% remain undiagnosed.

The etiology depends on age, duration of fever, and immunologic status. In children less than 6 years of age an infectious etiology is the most common cause. In children between the ages of 6 and 16, collagen vascular disease and inflammatory bowel disease increase in prevalence. In the elderly there is a higher percentage of patients with giant cell arteritis and "cryptic" disseminated tuberculosis. Fewer cases are undiagnosed, and such diseases as atrial myxoma, systemic lupus, factitious fever, and adult Still's disease have not been reported to cause FUO in the elderly.

As a generalization, the longer the duration of an FUO, the less likely are infectious and neoplastic etiologies, whereas factitious disease, granulomatous diseases, Still's disease, and other, more obscure diseases become important considerations.

The evaluation of the patient with FUO (Table 211.5) is challenging and should be guided by clinical observation, physical examination, and a knowledge of the common causes. Diagnostic procedures should not substitute for daily reassessment. If the initial "FUO work-up" is negative, mentally "readmitting" the patient, carefully reviewing the data, repeating technically inadequate or equivocal studies, discussing the case with consultants and colleagues, and considering the possibility that you are being misled by a false-negative or false-positive test result may help lead to the diagnosis.

A comment is necessary on factitious fever and fraudulent infection. A significant number of patients with FUO have self-induced disease. These patients are usually female health professionals. Clues to the diagnosis are listed in Table 211.6.

Night sweats may occur with any condition causing fever. Although suggestive of tuberculosis or lymphoma, they also occur in brucellosis, lung abscess, bacterial endocarditis, diabetic autonomic neuropathy, nocturnal hypoglycemia, nocturnal angina, and diabetes insipidus.

Except in patients with underlying heart disease, moderate fever has no deleterious effects on the patient. Antipyretics, in addition to clouding the issue, make the patient uncomfortable because of periods of sweating when the antipyretic is given and chills when the effect of the agent is wearing off. If antipyretics are used, they should be given around the clock (e.g., every 3 to 4 hr) rather than as needed in response to symptoms, to avoid this rollercoaster effect.

High fevers can be dangerous to the central nervous system, particularly in children. A sustained temperature greater than 42°C may lead to permanent brain damage. Febrile convulsions in children are common with temperatures greater than 41°C. Survival is rare at temperatures greater than 43°C. These elevations of temperature require heroic measures. Antipyretics and cooling blankets rarely are adequate. Measures found to be efficacious include immersing the patient in a cold water bath; placing wet ice bags over the major arteries of the groin and axilla while massaging the muscles with cool, wet sponges; and evaporative cooling methods which utilize large fans and continuous spraying of the body surface with tepid water such as with a body cooling unit. Although evaporative cooling techniques have been touted as being "more physiologic" than other techniques, have many practical advantages, and are now widely utilized, their superiority to ice-water immersive techniques in reducing morbidity and mortality in patients with hyperthermia or extreme pyrexia remains unproven.

Table 211.5
Procedures Employed in Work-up in the FUO

Laboratory tests
Cultures, serologies, lumbar puncture, ANA, RF, skin tests, etc.
Radiography
Chest x-ray, barium studies, IVP, bone scan, ultrasound, computerized tomography, MRI
Invasive procedures
Liver biopsy, bone marrow biopsy, exploratory laparotomy, skin lesion biopsy, lymph node biopsy

Table 211.6
Clues to the Diagnosis of Factitious Fever

History
Medical or paramedical training
Complicated history with multiple or prolonged hospitalizations (sometimes for FUO)
Inconsistencies in the history
No weight loss
Physical examination
Good general appearance or normal examination
Temperature >42°C (106°F)
Failure of temperature to follow normal diurnal variation
Absence of tachycardia despite high temperature
Wide swings in recorded temperature
Rapid defervescence with no diaphoresis
Cool skin
Morning "fever" only
No response to antipyretics
Elevated temperature that is always the same
Hospital course
Refusal to cooperate with routine temperature-taking procedures
Associated puzzling disorders
Personality disorder
Bedside instruments (heating pad, lighter, hot liquids)
Refusal to use an IVAC electronic thermometer
Unrevealing FUO evaluation
Polymicrobial bacteremia with no obvious source
Temperature of simultaneous freshly voided urine is normal

Source: Factitious or fraudulent fever. In: Murray HW, ed. FUO: fever of undetermined origin. New York: Futura, 1983;87–107. Reprinted with permission.

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